Drug use in renal and hepatic failure

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2007
Why?: increase ... incidence of renal failure
Why? Increase in (liver) failure ...
Why ? Multiple organ failure

- Sepsis, septic shock
  - Multiple organ failure
  - Shock
  - Liver-and kidney failure
- Burden of costs
Organ failure

- Pharmacokinetics
  - Absorption
  - Distribution
  - Metabolisation
  - Excretion
- Pharmacodynamics
Renal failure. It seems easy …

Drugs and their metabolites are excreted by the kidney
Problem 1: how to measure?

- Kidney function
  - normal 3-6 months after birth
  - Glomerular filtration rate (GFR)
    - = 120-140 ml/min
  - Age 65 years: 50-60 ml/min
Renal disease?

- Functional loss of nephrons
  - Acute:
    - shock
    - aminoglycosides
  - Chronic
Estimation

- Creatinine clearance
- Byproduct of muscle metabolism
The image depicts the biochemical pathway of creatine formation. The process begins with the conversion of "arginine" to "guanidinoacetate" in the kidney, catalyzed by "glycine amidinotransferase." Guanidinoacetate is then converted to "creatinine" nonenzymatically. An enzymatic step involving "S-adenosylmethionine" and "guanidinoacetate methyltransferase" occurs in the liver to produce "creatine." Creatine is then converted to "creatine phosphate" by "creatine kinase," utilizing "ATP" and "ADP."
Creatinine clearance

Incomplete collections …

\[ C = \frac{U \times V}{P} \]
Creatinine clearance

\[
\text{Creatinine Clearance} = \frac{(140 - \text{Age [y]}) \times \text{Lean Body Weight (kg)}*}{72 \times \text{Serum Creatinine (mg/dL)}},
\]

Cockroft and Gault method

Problems …

decreased muscle mass,
not stable creatinine,
not within 30 % of ideal body weight
… age
Problem 2:

- Nephron functional unit of the kidney
- Small molecules filtered glomerulus
- Reabsorption of drugs
  - pH, pKa, ionization, lipid-soluble
- Active secretion

\[ \text{pH} = \text{pKa} + \log \frac{B}{A} \]
One Nephron of the Kidney

Key
- Blood
- Tubular Fluid
- Small Particles
- Proteins

Renal Corpuscle
Bowman's Capsule
Glomerulus
U-Shaped Tubule
Collecting Duct

Filtration
Reabsorption
Secretion

Bowman's Capsule (Glomerular)
Filtration of smaller molecules

Proximal Tubule
Active secretion of weak electrolytes (especially acids) and reabsorption of water

Distal Tubule
Passive transfer of lipid soluble drugs and reabsorption of water

Loop of Henle
Reabsorption of water

Urine
Thanks to PENICILLIN  
...He Will Come Home!
Probenecid
Probenicid

Front shot, after 2 years roid free training

Front shot one year later after steroids

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Therefore …

- Creatinine clearance is a surrogate for glomerular filtration rate
- Estimation that
  - drug reabsorption
  - and excretion decline
    - parallel with the GFR
  - Intact nephron theory
  - Not always true
Surrogate endpoints

- When David Beckham leaves the field towards the end of a match, the man who replaces him is a surrogate
- Subrogare = to substitute
Classical story 1

- 60 year, woman, emergency department
- Bipolar disorder, 10 years, 2 x 300 mg Lithium/day
- 14 days before admission: hypertension, hydrochlorothiazide
- Tremor, rigidity, ataxia
- High sodium and chloride
- Metabolic acidosis
Happens?

- measure plasma lithium and hydrochlorothiazide concentrations?
  - Lithium 3 meq/l (nl up to 1.25)

- Reason Li intoxication?
  - A. increased intake?
  - B. interaction hydrochlorothiazide?
  - C. hypertension, decreased renal excretion and renal failure?
Answer …

- Thiazide diuretics: inhibitors Na+-CL- transport
- Lithium filtered
- Proximal tubulus:
  - reabsorption (70 %), exchange
- Thiazide diuretics: extracellular volume contraction, increased lithium reabsorption
  - Lisdiuretics: decline lithium reabsorption
Problem 3: dose or time adjustment

? What do you do ?

- Clearance < 50-60 ml/min: modest reduction
- < 25-30 ml/min: moderate reduction
- < 15 ml/min: substantial decrease
- Decrease the dose
- Prolong dosage interval
If drug dose is reduced: max drug concentration lower, minimal higher

If dosage interval is prolonged, maximum and minimum usually about the same

Average steady state is identical
How?

- Orally, only a limited number of solid dosage forms available
  - Increase dosage interval
  - Useful long-half lives
- Parenterally
  - A smaller dose can easily be given
  - Dosage reduction leads to more constant serum levels
- Narrow therapeutic index
  - Aminoglycosides or vancomycin
  - Target serum conc for maximum and minimum steady state
  - Both dose and dosage interval
Problem 4: non-renal clearance
Narrow therapeutic index

- Creatinine clearance for the individual patient
  - Clearance independent parameter
  - Straight line with a slope
Non-renal clearance = intercept with the Y-axis

Non-renal clearance digoxin 20 ml/min in severe heart failure, 40 ml/min mild or no heart failure
Non-renal clearance

- Not affected by renal failure
- Total body clearance can be measured by
  1. measuring the steady state drug level during a constant infusion of the drug
     - Clearance = infusion rate / steady state level
  2. area under the drug level vs time curve after a single dose
     - Clearance = dose / area under the drug level vs time
One can then calculate the dose of the drug for a patient with any degree of renal insufficiency from data obtained from normal subjects.

Nonrenal clearance / total body clearance x dose normal persons = anuric patients

Weakness: non-renal clearance not affected in renal failure.
Estimation of the elimination rate

However, dependent variable. Relies on clearance and VD \( ke = \frac{Cl}{V} \)
Elimination impaired …

- Metabolites of morphine
  - cause respiratory depression …
- Metabolites of meperidine
  - cause seizures …
- Accumulation of nitrofurantoin
  - causes neuropathy …
- A 69-year-old man, with renal and cardiac disease, was prescribed metformin due to failing glycaemic control on glibenclamide monotherapy. He was well for six weeks, then developed lactic acidosis and died within 3 days
  - Increased production and decreased clearance of lactate…
Problem 5: even absorption is altered in renal insufficiency …

- Slower gastric emptying (diabetics)
  - Edema in gi tract (renal insufficiency) slow absorption
- Iron and phosphate binders
- High gastric pH (antacids): slowing medication acid environment
- Al-or calcium containing antacids
  - Non-absorbable chelation products: digoxin
Problem 6: Volume of distribution
Plasma protein displacement

- By endogenous and exogenous substances that would normally be eliminated by the kidney

Loading dose same unless Vd altered
But volume of distribution is frequently altered …

- Depends on the size of the patient
- Patients with renal failure are smaller
  - Smaller VD
  - Higher plasma concentration
- Have abnormal albumin
  - Decreased
- Decreased tissue binding
  - Digoxin, decreased tissue binding,
  - Standard loading dose, higher drug level and greater intensity of effect
Protein binding

- Free plasma concentration of phenytoin increases from 0.1 to 0.35
- Observed plasma conc of 4 mg/l comparable tot 10-15 mg/l normal renal function
Hepatic metabolism is decreased in chronic renal failure

- Acetylation and ester hydrolysis slowed

No prediction possible

Phenytoin

- Increased metabolism, combined decreased protein binding
- Low total plasma drug level, normal therapeutic levels
- Renal failure: higher doses necessary
Moreover …

- An average of 8 different classes of drugs/patient are prescribed in patients with renal failure
- Greater risk of drug-drug interactions
Problem 8: interaction by itself leads to significant renal insufficiency

- pharmacodynamics
Case 1

- 55 year old man, BP 220/114
- Retrosternal pain
- Atenolol, lisinopril, nitroglycerine, creatinine
- 1.5 mg%
- diarrhea
- hospital 8.5 mg/dl creatinine, potassium 7.9 meq/l
The solution is easy …

- Hydrate, stop lisinopril, start amlodipine
- Without dialysis … recovery renal function
Case 2

- 67 year old man, arterial hypertension, EF 30 %, enalapril
- Creatinine 1.2 mg%, art BP 140/90 mm Hg
- Gout, indomethacine
Case 2

- 1 week later:
  - Generalised edema
  - ABP 180/95 mm Hg
  - Dyspnoe d’effort, orthopnea
  - Creatinine 4.0 mg/dl
Production and Actions of Prostaglandins and Thromboxane

Reason?

- Dehydration
- NSAIDs
  - Vasodilating PG’s decreased
Smets et al, 2007
Problem 10: Dialysis …

- Process whereby substances move via a concentration gradient across a semipermeable membrane
- Hemodialysis
- Peritoneal dialysis
- Substances small enough to pass through the pores in the semipermeable membrane: pass into dialysis fluid
So …

- Used to remove from the blood drug overdose
- Mostly coincidental to the removal of toxic waste products
CASe d-LACTATE

PROPYLENEGLYCOL

DL-lactaldehyde

Methylglyoxal

D-lactate

D-lactate

L-lactate: 39 mmol/l
L-lactate (VITROS): 1.4
D-lactate: 110 mmol/l
Dialysis …

- Renal failure
  - Only clearance is non-renal clearance
- Dialysis
  - Clearance non-renal and dialysis
- IF dialysis clearance > 30 % of total clearance
  - Considered significant
Drug characteristics affect dialysis removal?

- **Molecular size**
  - Most low flux, small pores
    - < 500 d eliminated (theophylline yes, aminoglycosides or digoxin no)
    - Blood flow, fluid flow, surface area membrane
  - High flux: vancomycin also removed
    - Previously considered not to be removable

- **Water/lipid solubility**
- **Plasma protein binding**
- **Vd:**
Vd:

- May clear the serum, but when dialysis is completed
  - Rebound effect (digoxin)
Hemodialysis
Hemodialysis

- Artificial kidney: dialysis fluid 400-600 ml/min
- Since mid 1980s: FDA required pharmacokinetic studies when renally eliminated drugs
  - Patients requiring chronic hemodialysis
Dialysis clearance

Calculation of dialysis clearance ...

\[ \text{ER} = \frac{C_{\text{in}} - C_{\text{out}}}{C_{\text{in}}} \]

\[ \text{Cl} = Q(\text{ER}) \]

Blood flow = 300–400 mL/min

Dialysis fluid = 400–600 mL/min
Example

- Loading dose?
- \( LD = C_{\text{max}} \times V \)
- Expected elimination constant for a creatinine clearance of zero
  - Calculate concentration prior to dialysis
- Half-life of many drugs during dialysis is known ...
Hemodialysis clearance ...
Example ...

Meropenem

- Usually 1 g 8h
- Anuria
  - 500 mg /24 h
  - 500 mg after dialysis …
Peritoneal dialysis
Peritoneal dialysis

- Gaining in popularity
- Peritoneal membrane used as semipermeable membrane
- Dialysis fluid periodically removed
- Outpatient
Peritoneal dialysis

- Removes drug much less efficiently
- Less likely to replace during intermittent peritoneal dialysis
- Only receive long term peritoneal dialysis
- Example
  - Half-life aminoglycosides end stage renal failure 50 h
  - Hemodialysis 4 h
  - PD 36 hours
Peritoneal dialysis

- Usual methods of measuring serum concentration and dosage adjustment require little or no modification
  - Simply another clearance mechanism taking place in the patient’s body

- Drugs can be added to the peritoneal dialysis fluid
  - Insulin f.i.
  - Antibiotics: peritonitis
  - … be careful: peritonitis: more drugs absorbed
Take home message …

- Creatinine clearance
- Absorption and secretion of drugs
- Dose or the interval
- Prostaglandins: pharmacodynamics
- Absorption, distribution, metabolisation
- Hemodialysis, clearance > 30 %
- Peritoneal dialysis: continuous
Hepatic failure
CYP...

- Families and subfamilies/ amino acid sequence
- > 40 % identity: number (ar., rom.)
- > 55 % identity, subfamily, CAPITAL
- Individual gene, arabic number
- CYP2D6
- 270 CYP gene families, 18 mammals
- rice: 324 functional CYP genes
- Continu INTERNET: www.imm.ki.se/CYPalleles/
Past ...

- mixed function oxidases, liver, exogenous substrates
- Oxidation, reduction, peroxidation ...
- Phase I
- Phase II: glucuronic acid, sulphate
Present in many organ systems …

- Kidney: distal tubuli
- Small bowel: villi
- Lung: Clara cell
- Endothelium
  - Vascular homeostasis
  - homeostasis CYP epoxygenase : NO and Pgl2 VD
- Liver …
2 IMPORTANT

- CYP2C9
- CYP3A4
Inhibition

- Inhibition CYP isoenzyme: decreased metabolism, increased serum concentration
Inhibition

- **CYP2C9**
  - Cimetidine, (omeprazole)
  - Fluoxetine
  - Amiodarone
  - Chloramphenicol, trimethoprim
  - Fluconazole
  - Fluvastatin
Inhibition

- CYP3A4
  - Grape fruit
  - Cyclosporine
  - Antiviral (retro)
  - Amiodarone
  - Diltiazem
  - Erythromycin, clarithromycin
  - Fluconazole
Inhibition both

- Azoles …
- Amiodarone
Induction

- Inductie CYP isoenzyme: increased metabolism
- Decreased serum concentration substrate
Induction

- **CYP2C9**
  - Ethanol
  - Rifamycins
  - Anti-epileptic agents; carbamazepine, phenobarbital, diphenylhydantoin
Induction

- **CYP3A4**
  - Carbamazepine, phenobarbital, fenytoine
  - Glucocorticoids
  - Rifamycins
Induction both

- Anti-epileptic agents
- Rifamycins
- Hypericum perforatum
Drugs metabolised by CYP ...

- **CYP2C9**
  - Carvedilol, losartan, ibuprofen, phenytoine, TCA, s-warfarine, ticlopidine...

- **CYP3A4**
  - Amiodarone, clarithromycin, losartan, lovastatin, simvastatin, atorvastatin, tcad, r-warfarine, verapamil, cisapride, tacrolimus, ...
Example … induction QT-prolongation

- Cisapride-clarithromycin (eradication Helicobacter); torsades de pointe
Disasters … ?

- Mibefradil, calcium blocking agents …
- Terfenadine
- Astemizole
- Cisapride
- cerivastatin (Baycol en Lipobay) and gemfibrozil
Interactions

- More interactions in liver failure/insufficiency
  - When already decreased CYP activity is present?
Equation hepatic metabolism

- Contains liver blood flow, fraction of unbound drug in the blood, intrinsic clearance
- Orally administered drugs pass through the liver
  - 1/3 hepatic artery, 2/3 portal vein (first pass effect)
- Elimination unchanged in the bile
Organ Clearance = \frac{Q \cdot (C_a - C_v)}{C_a} = Q \cdot E

\[ CL_H = Q \cdot \frac{fu \cdot CL_{int}}{(Q + fu \cdot CL_{int})} = \frac{Q \cdot CL_{int}^{total}}{Q + CL_{int}^{total}} \]

Wilkinson, 1975
Based on this formula

- Flow limited drugs: not dependent on protein binding
  - Morphine
- Capacity limiting drugs: independent of blood flow, but on protein binding
  - Phenytoine, warfarine
- In between
  - Theophylline
Very complex ....

- **Low extraction rate** (100 % liver metabolised)
  - Numeric value of LBF very high
  - Hepatic clearance = free fraction blood x intrinsic clearance

- **High extraction rate**
  - Liver blood flow much less
  - Hepatic clearance = liver blood flow
Chronic Cirrhosis

1. Simultaneous decrease in hepatic clearance and liver first pass effect
   - Extreme large steady state concentrations of orally administered drugs

2. Further decrease blood flow (hepatocytes replaced by nonfunctional connective tissue)

3. Liver produces albumin and α1-acid glycoprotein
   - Free fraction increases
   - Moreover high amounts of bilirubin displaces drugs from protein binding

4. $ke = \frac{Cl}{V}$, elimination rate constant declines
Increased free fraction (if highly protein bound) will alter

- Hepatic clearance
- Renal drug clearance
- Vd

As $K_e = C_l/V$

- It almost always decreases
Same problems …

- Creatinine clearance
- No single laboratory test
  - Child-Plugh classification
Child Plugh score

- **Total Serum Bilirubin**
  - Bilirubin <2 mg/dl: 1 point
  - Bilirubin 2-3 mg/dl: 2 points
  - Bilirubin >3 mg/dl: 3 points

- **Serum Albumin**
  - Albumin >3.5 g/dl: 1 point
  - Albumin 2.8 to 3.5 g/dl: 2 point
  - Albumin <2.8 g/dl: 3 point

- **INR**
  - INR <1.70: 1 point
  - INR 1.71 to 2.20: 2 point
  - INR >2.20: 3 point

- **Ascites**
  - No Ascites: 1 point
  - Ascites controlled medically: 2 point
  - Ascites poorly controlled: 3 point

- **Encephalopathy**
  - No Encephalopathy: 1 point
  - Encephalopathy controlled medically: 2 point
  - Encephalopathy poorly controlled: 3 point
- **Score 8-9**
  - Moderately decreased in initial daily dosage
- **Score > 10**
  - 50% decrease
- **Example …**
  - Antifungal agents fluconazole, voriconazole, caspofungin…
    - All decreased dosage in liver failure or insufficiency
Example

- 95% liver metabolised
- 500 mg/6 hours
- Child-Pugh score of 12
  - 1000 mg/d
  - 250 mg/6 h
  - 500 mg/12 h
Again ... 

If drug dose is reduced: max drug concentration lower, minimal higher
If dosage interval is prolonged, maximum and minimum usually about the same

Average steady state is identical
Other pharmacokinetic parameters

- Absorption
  - Vitamin A, D, E, K
- Distribution
  - Albumin, Vd
- Excretion
  - Bile
- Pharmacodynamics
  - Benzodiazepines...
Example

- Theophylline
  - Children
    - 1.4 ml/min/kg clearance
    - Mean dose 0.8 mg/kg/h
  - Adults
    - Clearance 0.7 ml/min/kg
    - Mean dose 0.4 mg/kg/h
  - Cirrhosis
    - Clearance 0.35 ml/kg/h
    - Mean dose 0.2 ml/kg/h

- Calculation
  - Maintenance dose = steady-state conc x drug clearance
  - Steady state 8 – 12 mg/l
Take home message ...

- Hepatic failure: dose and interval
- Metabolism
- Child Plugh score
- Absorption, distribution, excretion ...
Kidney and liver failure

- F DA
- A bsorption, distribution, metabolisation ...
- I ncidence increasing ...
- L egal aspects ...
- U rinary indices
- R enal/hepatic clearance
- E uropean Summer School